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FILE 'SCISEARCH' ENTERED AT 13:41:01 ON 07 MAY 2008

FILE 'TEXTILETECH' ENTERED AT 13:41:01 ON 07 MAY 2008

FILE 'USPATFULL' ENTERED AT 13:41:01 ON 07 MAY 2008

FILE 'USPATOLD' ENTERED AT 13:41:01 ON 07 MAY 2008

FILE 'USPAT2' ENTERED AT 13:41:01 ON 07 MAY 2008

FILE 'WPIDS' ACCESS NOT AUTHORIZED

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FILE 'WSCA' ENTERED AT 13:41:01 ON 07 MAY 2008

FILE 'WTEXTILES' ENTERED AT 13:41:01 ON 07 MAY 2008

FILE 'BIOSIS' ENTERED AT 13:41:01 ON 07 MAY 2008

FILE 'EMBASE' ENTERED AT 13:41:01 ON 07 MAY 2008

FILE 'MEDLINE' ENTERED AT 13:41:01 ON 07 MAY 2008

```
=> s VNP40110M
L1           0 VNP40110M

=> s methylaminocarbonyl(a)hydrazine
L2          17 METHYLAMINOCARBONYL(A) HYDRAZINE

=> s l2 and VNP40101M
L3          17 L2 AND VNP40101M

=> s l3 and (tumor or antitumor)
L4          17 L3 AND (TUMOR OR ANTITUMOR)

=> s l4 and nucleoside
L5           2 L4 AND NUCLEOSIDE

=> dis l4 1-17 bib abs

L4   ANSWER 1 OF 17  CAPLUS  COPYRIGHT 2008 ACS on STN
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AN 2005:1354137 CAPLUS
DN 144:381446
TI The antineoplastic efficacy of the prodrug Cloretazine is produced by the synergistic interaction of carbamoylating and alkylating products of its activation
AU Baumann, Raymond P.; Seow, Helen A.; Shyam, Krishnamurthy; Penketh, Philip G.; Sartorelli, Alan C.
CS Department of Pharmacology and Developmental Therapeutics Program, Cancer Center, Yale University of Medicine, New Haven, CT, 06520, USA
SO Oncology Research (2005), 15(6), 313-325
CODEN: ONREE8; ISSN: 0965-0407
PB Cognizant Communication Corp.
DT Journal
LA English
AB Cloretazine {1,2-bis(methylsulfonyl)-1-[(2-chloroethyl)-2-(methylamino)carbonyl]hydrazine; VNP40101M; 101M} is a sulfonylhydrazine prodrug that possesses broad spectrum antitumor efficacy against transplanted murine and human tumor models and has shown activity in clin. trials against relapsed or refractory acute myeloid leukemia. Base catalyzed activation of this prodrug generates two different reactive intermediates: chloroethylating species that covalently interact with DNA at the O6-position of guanine residues that progress to a G-C interstrand cross-link, and a carbamoylating agent, Me isocyanate. Previous findings from this laboratory have provided initial evidence that Me isocyanate can contribute to the efficacy of Cloretazine by enhancing the cytotoxicity of the generated chloroethylating species. This action may be due in part to inhibition of the DNA repair protein O6-alkylguanine-DNA alkyltransferase (AGT); however, activity in cells devoid of AGT indicates that other actions are involved in the synergistic cytotoxicity. Herein we demonstrate that O6-benzylguanine can also produce synergistic cell kill with the alkylating component of Cloretazine but differs from Me isocyanate in that the enhancement occurs in AGT-containing cells, but not in cells devoid of AGT. Me isocyanate generated by the decomposition of 1,2-bis(methylsulfonyl)-1-[methylaminocarbonyl]hydrazine also acts to enhance the activity of a variety of DNA crosslinking agents, while only producing additive cytotoxicity with methylating agents. How cytometric studies using annexin as a marker for apoptosis indicate that in Chinese hamster ovary cells and in human leukemia cells Cloretazine-induced apoptosis is primarily caused by the generated Me isocyanate. Comet assays designed to detect DNA cross-links in intact cells indicate that the chloroethylating species generated by the activation of Cloretazine produce DNA cross-links, with the co-generated Me isocyanate increasing the degree of crosslinking produced by the reactive chloroethylating species. These findings provide further evidence that the Me isocyanate produced by the activation of Cloretazine can be a major contributor to the cytotoxicity produced by this antineoplastic agent.
RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:304344 CAPLUS
DN 137:288588
TI Toxicological evaluation of 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl)hydrazine (VNP40101M), a novel alkylating agent with potential antitumor activity, with intravenous administration in rats and dogs
AU Lee, King C.; Almassian, Bijan; Noveroske, James
CS Vion Pharmaceuticals, Inc., New Haven, CT, USA
SO International Journal of Toxicology (2002), 21(1), 23-38
CODEN: IJTOFN; ISSN: 1091-5818

PB Taylor & Francis Ltd.
DT Journal
LA English
AB These studies investigated the toxicol. effects of 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl) hydrazine, VNP40101M, a novel alkylating antitumor agent, in animals. Sprague-Dawley rats (2-10/sex/time point at each dose) and Beagle dogs (1-3/sex/time point at each dose) were treated with VNP40101M (0 [vehicle], 1, 3, 10, and 20 mg/kg in rats and 0, 0.3, 1, and 3 mg/kg in dogs), given i.v. (IV, bolus via the tail or slow push via the cephalic or saphenous vein, resp.) once daily for 5 consecutive days. Clin. signs, mortality, body weight, clin. pathol., gross necropsy, organ wts., and histopathol. were evaluated for as long as 43 days in rats and 50 days in dogs. In rats, the toxic doses were found to be at 10 and 20 mg/kg, which induced mainly pulmonary toxicity and mortality. The pulmonary toxicity was reflected by an increase in lung weight; clear, pink or red fluid within the thoracic cavity observed at necropsy; and histopathol. evidence of alveolar edema, vascular congestion, alveolar histiocytosis, and vascular thrombi. Although some of these effects were observed in rats treated with 3 mg/kg, the incidence was low (.apprx.7%-30%) and may be reversible (based on the time-dependent reduction in the magnitude of lung weight increases). Therefore, the maximum tolerated dose (MTD, or the maximum dose that did not induce significant toxicity or induced reversible toxicity) was ≥3 mg/kg. VNP40101M at 1 mg/kg did not induce any toxicity, other than low incidence of alveolar edema (2/30 rats), and increased incidences of capillary ectasis/congestion and alveolar histiocytosis (2-6/30 rats vs. 1/30-36 in control rats). Therefore, the low effect level (LOEL) is considered to be 1 mg/kg in rats when given IV for 5 days. In dogs, LOEL, MTD, and toxic dose levels were comparable (based on a body weight/surface area conversion) to those in rats, except for some gastrointestinal (GI) effects (i.e., red lesion in the ileum) observed at 0.3 mg/kg (equivalent to 1 mg/kg, or similar to the LOEL in rats) and the associated effects (slight body weight loss and inappetence). For dogs treated with 1 mg/kg (equivalent to .apprx.3 mg/kg, or MTD, in rats), VNP40101M induced the same GI effects seen in dogs treated with 0.3 mg/kg of VNP40101M. Addnl., a transient reduction in white blood cell counts was also observed Three mg/kg (equivalent to .apprx.10 mg/kg, or toxic dose level, in rats) was toxic to dogs, as reflected by the poor clin. condition of these dogs, which subsequently required euthanasia. In conclusion, VNP40101M, when given IV once daily for 5 consecutive days, has a LOEL of 1 mg/kg, a MTD of 3 mg/kg, and toxic doses at ≥10 mg/kg in rats. The primary toxicity of VNP40101M was pulmonary toxicity and mortality. Based on an interspecies body weight/surface area conversion, VNP40101M had comparable LOEL (0.3 mg/kg), MTD (1 mg/kg), and toxic doses (≥3 mg/kg) in dogs, except that dogs appeared to be more sensitive to the GI effects of VNP40101M.
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 17 PASCAL COPYRIGHT 2008 INIST-CNRS. ALL RIGHTS RESERVED. on STN
AN 2006-0030302 PASCAL

TIEN The antineoplastic efficacy of the prodrug Cloretazine is produced by the synergistic interaction of carbamoylating and alkylating products of its activation
AU BAUMANN Raymond P.; SEOW Helen A.; SHYAM Krishnamurthy; PENKETH Philip G.; SARTORELLI Alan C.

CS Department of Pharmacology and Developmental Therapeutics Program, Cancer Center, Yale University School of Medicine, New Haven, CT 06520, United States
SO Oncology research, (2005), 15(6), 313-325, 25 refs.
ISSN: 0965-0407
DT Journal
BL Analytic
CY United States
LA English
AV INIST-21955, 354000135061190040

AB Cloretazine 1,2-bis(methylsulfonyl)-1-[(2-chloroethyl)-2-(methylamino)carbonyl]hydrazine; VNP40101M; 101M is a sulfonylhydrazine prodrug that possesses broad spectrum antitumor efficacy against transplanted murine and human tumor models and has shown activity in clinical trials against relapsed or refractory acute myeloid leukemia. Base catalyzed activation of this prodrug generates two different reactive intermediates: chloroethylating species that covalently interact with DNA at the O.sup.6-position of guanine residues that progress to a G-C interstrand cross-link, and a carbamoylating agent, methyl isocyanate. Previous findings from this laboratory have provided initial evidence that methyl isocyanate can contribute to the efficacy of Clore-tazine by enhancing the cytotoxicity of the generated chloroethylating species. This action may be due in part to inhibition of the DNA repair protein O.sup.6-alkylguanine-DNA alkyltransferase (AGT); however, activity in cells devoid of AGT indicates that other actions are involved in the synergistic cytotoxicity. Herein we demonstrate that O.sup.6-benzylguanine can also produce synergistic cell kill with the alkylating component of Cloretazine but differs from methyl isocyanate in that the enhancement occurs in AGT-containing cells, but not in cells devoid of AGT. Methyl isocyanate generated by the decomposition of 1,2-bis(methylsulfonyl)-1-[methylaminocarbonyl]hydrazine also acts to enhance the activity of a variety of DNA cross-linking agents, while only producing additive cytotoxicity with methylating agents. Flow cytometric studies using annexin as a marker for apoptosis indicate that in Chinese hamster ovary cells and in human leukemia cells Cloretazine-induced apoptosis is primarily caused by the generated methyl isocyanate. Comet assays designed to detect DNA cross-links in intact cells indicate that the chloroethylating species generated by the activation of Cloretazine produce DNA cross-links, with the co-generated methyl isocyanate increasing the degree of cross-linking produced by the reactive chloroethylating species. These findings provide further evidence that the methyl isocyanate produced by the activation of Cloretazine can be a major contributor to the cytotoxicity produced by this antineoplastic agent.

L4 ANSWER 4 OF 17 PASCAL on STN
AN 2002-0285439 PASCAL

TIEN Toxicological evaluation of 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl)hydrazine (VNP40101M), a novel alkylating agent with potential antitumor activity, with intravenous administration in rats and dogs
AU LEE King C.; ALMASSIAN Bijan; NOVEROSKE James
CS Vion Pharmaceuticals, Inc., New Haven, Connecticut, United States; Oread Inc., Farmington, Connecticut, United States
SO International journal of toxicology, (2002), 21(1), 23-38, 6 refs.
ISSN: 1091-5818
DT Journal

BL Analytic
CY United Kingdom
LA English
AV INIST-20351, 354000100837080030

AB These studies investigated the toxicological effects of 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl) hydrazine, VNP40101M, a novel alkylating antitumor agent, in animals. Sprague-Dawley rats (2-10/sex/time point at each dose) and Beagle dogs (1-3/sex/time point at each dose) were treated with VNP40101M (0 [vehicle], 1, 3, 10, and 20 mg/kg in rats and 0, 0.3, 1, and 3 mg/kg in dogs), given intravenously (IV, bolus via the tail or slow push via the cephalic or saphenous vein, respectively) once daily for 5 consecutive days. Clinical signs, mortality, body weight, clinical pathology, gross necropsy, organ weights, and histopathology were evaluated for as long as 43 days in rats and 50 days in dogs. In rats, the toxic doses were found to be at 10 and 20 mg/kg, which induced mainly pulmonary toxicity and mortality. The pulmonary toxicity was reflected by an increase in lung weight; clear, pink or red fluid within the thoracic cavity observed at necropsy; and histopathological evidence of alveolar edema, vascular congestion, alveolar histiocytosis, and vascular thrombi. Although some of these effects were observed in rats treated with 3 mg/kg, the incidence was low (.eqvsim.7%-30%) and may be reversible (based on the time-dependent reduction in the magnitude of lung weight increases). Therefore, the maximum tolerated dose (MTD, or the maximum dose that did not induce significant toxicity or induced reversible toxicity) was >=3 mg/kg. VNP40101M at 1 mg/kg did not induce any toxicity, other than low incidence of alveolar edema (2/30 rats), and increased incidences of capillary ectasis/congestion and alveolar histocytosis (2-6/30 rats vs. 1/30-36 in control rats). Therefore, the low effect level (LOEL) is considered to be 1 mg/kg in rats when given IV for 5 days. In dogs, LOEL, MTD, and toxic dose levels were comparable (based on a body weight/surface area conversion) to those in rats, except for some gastrointestinal (GI) effects (i.e., red lesion in the ileum) observed at 0.3 mg/kg (equivalent to 1 mg/kg, or similar to the LOEL in rats) and the associated effects (slight body weight loss and inappetence). For dogs treated with 1 mg/kg (equivalent to .eqvsim.3 mg/kg, or MTD, in rats), VNP40101M induced the same GI effects seen in dogs treated with 0.3 mg/kg of VNP40101M. Additionally, a transient reduction in white blood cell counts was also observed. Three mg/kg (equivalent to .eqvsim.10 mg/kg, or toxic dose level, in rats) was toxic to dogs, as reflected by the poor clinical condition of these dogs, which subsequently required euthanasia. In conclusion, VNP40101M, when given IV once daily for 5 consecutive days, has a LOEL of 1 mg/kg, a MTD of 3 mg/kg, and toxic doses at >=10 mg/kg in rats. The primary toxicity of VNP40101M was pulmonary toxicity and mortality. Based on an interspecies body weight/surface area conversion, VNP40101M had comparable LOEL (0.3 mg/kg), MTD (1 mg/kg), and toxic doses (>3 mg/kg) in dogs, except that dogs appeared to be more sensitive to the GI effects of VNP40101M.

L4 ANSWER 5 OF 17 SCISEARCH COPYRIGHT (c) 2008 The Thomson Corporation on STN
AN 2005:1228330 SCISEARCH
GA The Genuine Article (R) Number: 989TF
TI The antineoplastic efficacy of the prodrug Cloretazine (TM) is produced by the synergistic interaction of carbamoylating and alkylating products of its activation
AU Baumann R P; Seow H A; Shyam K; Penketh P G; Sartorelli A C (Reprint)
CS Yale Univ, Sch Med, Dept Pharmacol, 333 Cedar St, New Haven, CT 06520 USA

(Reprint); Yale Univ, Sch Med, Dept Pharmacol, New Haven, CT 06520 USA; Yale Univ, Sch Med, Dev Therapeut Program, Ctr Canc, New Haven, CT 06520 USA
alan.sartorelli@yale.edu
CYA USA
SO ONCOLOGY RESEARCH, (2005) Vol. 15, No. 6, pp. 313-325.
ISSN: 0965-0407.
PB COGNIZANT COMMUNICATION CORP, 3 HARTSDALE ROAD, ELMSFORD, NY 10523-3701 USA.
DT Article; Journal
LA English
REC Reference Count: 25
ED Entered STN: 15 Dec 2005
Last Updated on STN: 15 Dec 2005
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Cloretazine (TM) {1,2-bis(methylsulfonyl)-1-[(2-chloroethyl)-2-(methylamino)carbonyl]hydrazine; VNP40101M; 101M}) is a sulfonylhydrazine prodrug that possesses broad spectrum antitumor efficacy against transplanted murine and human tumor models and has shown activity in clinical trials against relapsed or refractory acute myeloid leukemia. Base catalyzed activation of this prodrug generates two different reactive intermediates: chloroethylating species that covalently interact with DNA at the O-6-poSition of guanine residues that progress to a G-C interstrand cross-link, and a carbamoylating agent, methyl isocyanate. Previous findings from this laboratory have provided initial evidence that methyl isocyanate can contribute to the efficacy of Cloretazinc (TM) by enhancing the cytotoxicity of the generated chloroethylating species. This action may be due in part to inhibition of the DNA repair protein O-6-alkylguanine-DNA alkyltransferase (AGT); however, activity in cells devoid of AGT indicates that other actions are involved in the synergistic cytotoxicity. Herein we demonstrate that O-6-benzylguanine can also produce synergistic cell kill with the alkylating component of Cloretazine (TM) but differs from methyl isocyanate in that the enhancement occurs in AGT-containing cells, but not in cells devoid of AGT. Methyl isocyanate generated by the decomposition of 1,2-bis(methylsulfonyl)-1[methylaminocarbonyl] hydrazine also acts to enhance the activity of a variety of DNA cross-linking agents, while only producing additive cytotoxicity with methylating agents. How cytometric studies using annexin as a marker for apoptosis indicate that in Chinese hamster ovary cells and in human leukemia cells Cloretazine (TM)-induced apoptosis is primarily caused by the generated methyl isocyanate. Comet assays designed to detect DNA cross-links in intact cells indicate that the chloroethylating species generated by the activation of Cloretazine (TM) produce DNA cross-links, with the co-generated methyl isocyanate increasing the degree of cross-linking produced by the reactive chloroethylating species. These findings provide further evidence that the methyl isocyanate produced by the activation of Cloretazine (TM) can be a major contributor to the cytotoxicity produced by this antineoplastic agent.

L4 ANSWER 6 OF 17 SCISEARCH COPYRIGHT (c) 2008 The Thomson Corporation on STN
AN 2002:257851 SCISEARCH
GA The Genuine Article (R) Number: 531HV
TI Toxicological evaluation of 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl) hydrazine (VNP40101M), a novel alkylating agent with potential antitumor activity, with intravenous administration in rats and dogs
AU Lee K C (Reprint); Almassian B; Noveroske J
CS Alton Pharma Inc, 777 Old Saw Mill River Rd, Tarrytown, NY 10591 USA (Reprint); Vion Pharmaceut Inc, New Haven, CT USA; Oread Inc, Farmington,

CT USA
CYA USA
SO INTERNATIONAL JOURNAL OF TOXICOLOGY, (JAN 2002) Vol. 21, No. 1, pp. 23-38. ISSN: 1091-5818.
PB TAYLOR & FRANCIS INC, 325 CHESTNUT ST, SUITE 800, PHILADELPHIA, PA 19106 USA.
DT Article; Journal
LA English
REC Reference Count: 6
ED Entered STN: 5 Apr 2002
Last Updated on STN: 5 Apr 2002
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB These studies investigated the toxicological effects of 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl) hydrazine, VNP40101M, a novel alkylating antitumor agent, in animals. Sprague-Dawley rats (2-10/sex/time point at each dose) and Beagle dogs (1-3/sex/time point at each dose) were treated with VNP40101M (0 [vehicle], 1, 3, 10, and 20 mg/kg in rats and 0, 0.3, 1, and 3 mg/kg in dogs), given intravenously (IV, bolus via the tail or slow push via the cephalic or saphenous vein, respectively) once daily for 5 consecutive days. Clinical signs, mortality, body weight, clinical pathology, gross necropsy, organ weights, and histopathology were evaluated for as long as 43 days in rats and 50 days in dogs. In rats, the toxic doses were found to be at 10 and 20 mg/kg, which induced mainly pulmonary toxicity and mortality. The pulmonary toxicity was reflected by an increase in lung weight; clear, pink or red fluid within the thoracic cavity observed at necropsy; and histopathological evidence of alveolar edema, vascular congestion, alveolar histiocytosis, and vascular thrombi. Although some of these effects were observed in rats treated with 3 mg/kg, the incidence was low (similar to7%-30%) and may be reversible (based on the time-dependent reduction in the magnitude of lung weight increases). Therefore, the maximum tolerated dose (MTD, or the maximum dose that did not induce significant toxicity or induced reversible toxicity) was, 3 mg/kg. VNP40101M at 1 mg/kg did not induce any toxicity, other than low incidence of alveolar edema (2/30 rats), and increased incidences of capillary ectasis/congestion and alveolar histocytosis (2-6/30 rats vs. 1/30-36 in control rats). Therefore, the low effect level (LOEL) is considered to be 1 mg/kg in rats when given IV for 5 days. In dogs, LOEL, MTD, and toxic dose levels were comparable (based on a body weight/surface area conversion) to those in rats, except for some gastrointestinal (GI) effects (i.e., red lesion in the ileum) observed at 0.3 mg/kg (equivalent to 1 mg/kg, or similar to the LOEL in rats) and the associated effects (slight body weight loss and inappetence). For dogs treated with 1 mg/kg (equivalent to similar to3 mg/kg, or MTD, in rats), VNP40101M induced the same GI effects seen in dogs treated with 0.3 mg/kg of VNP40101M. Additionally, a transient reduction in white blood cell counts was also observed. Three mg/kg (equivalent to similar to10 mg/kg, or toxic dose level, in rats) was toxic to dogs, as reflected by the poor clinical condition of these dogs, which subsequently required euthanasia. In conclusion, VNP40101M, when given IV once daily for 5 consecutive days, has a LOEL of 1 mg/kg, a MTD of 3 mg/kg, and toxic doses at, 10 mg/kg in rats. The primary toxicity of VNP40101M was pulmonary toxicity and mortality. Based on an interspecies body weight/surface area conversion, VNP40101M had comparable LOEL (0.3 mg/kg), MTD (1 mg/kg), and toxic doses (greater than or equal to3 mg/kg) in dogs, except that dogs appeared to be more sensitive to the GI effects of VNP40101M.

L4 ANSWER 7 OF 17 USPATFULL on STN
AN 2008:29697 USPATFULL

TI Combination Therapy Comprising Cloretazine
IN King, Ivan, North Haven, CT, UNITED STATES
Sznol, Mario, Woodbridge, CT, UNITED STATES
Belcourt, Michael, Wallingford, CT, UNITED STATES
Zheng, Li-Mou, Orange, CT, UNITED STATES
PI US 2008025984 A1 20080131
AI US 2005-593217 A1 20050325 (10)
WO 2005-US10152 20050325
20060915 PCT 371 date
PRAI US 2004-556565P 20040326 (60)
DT Utility
FS APPLICATION
LREP Law Offices of Albert Wai-Kit Chan, World Plaza, Suite 604, 141-07 20th Avenue, Whitestone, NY, 11357, US
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 599
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides a method for treating tumor in a subject comprising administering to the subject an effective amount of: (1) VNP40101M, or its equivalent; and (2) a nucleoside, or a nucleoside analog. This invention also provides a method for inhibiting tumor cell growth comprising contacting the tumor cell with effective amounts of: (1) VNP40101M, or its equivalent; and (2) a nucleoside, or a nucleoside analog. The present invention relates to the treatment of cancer, comprising administering to a subject in need thereof an effective amount of VNP40101M in combination with a nucleoside.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 8 OF 17 USPATFULL on STN
AN 2005:50445 USPATFULL
TI Water-soluble SHPs as novel alkylating agents
IN Lin, Xu, Branford, CT, UNITED STATES
Doyle, Terrence W., Killingworth, CT, UNITED STATES
King, Ivan, North Haven, CT, UNITED STATES
PA VION PHARMACEUTICALS, INC., New Haven, CT (U.S. corporation)
PI US 2005043244 A1 20050224
AI US 2004-950890 A1 20040927 (10)
RLI Division of Ser. No. US 2003-461282, filed on 13 Jun 2003, PENDING
DT Utility
FS APPLICATION
LREP Henry D. Coleman, 714 Colorado Avenue, Bridgeport, CT, 06605-1601
CLMN Number of Claims: 52
ECL Exemplary Claim: CLM-01-22
DRWN 15 Drawing Page(s)
LN.CNT 1684
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to compounds according to the structure (I): ##STR1##

Where R is --CH.sub.3 or --CH.sub.2CH.sub.2Cl; R' is C.sub.1-C.sub.7 alkyl or --CH.sub.2CH.sub.2Cl; R.sub.2 or R.sub.4 is OP0.sub.3H.sub.2, N0.sub.2, OCO(Glu-OH), NHCO(Glu-OH), NHR.sub.7 and unassigned groups of R.sub.2, R.sub.3, R.sub.4, R.sub.5 and R.sub.6 are, independently, H, F, Cl, Br, I, OH, OP0.sub.3H.sub.2, OCH.sub.3, CF.sub.3, OCF.sub.3, NO.sub.2, CN, SO.sub.2CH.sub.3, SO.sub.2CF.sub.3, COCH.sub.3, COOCH.sub.3, SCH.sub.3, SFs, NH.sub.2, NHR.sub.7, N(CH.sub.3).sub.2, OPO.sub.3H.sub.2, or a C1-C7 alkyl group with the proviso that when any

two of unassigned groups of R.sub.2, R.sub.3, R.sub.4, R.sub.5 or R.sub.6 are other than H, the other two of unassigned groups of R.sub.2, R.sub.3, R.sub.4, R.sub.5 or R.sub.6 are H. R.sub.7 is H or polyglutamyl as described. Phosphoric acid and glutamic acid can be a free acid or pharmaceutically acceptable salt thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 9 OF 17 USPATFULL on STN
AN 2004:321449 USPATFULL
TI WATER-SOLUBLE SHPS AS NOVEL ALKYLATING AGENTS
IN Lin, Xu, Branford, CT, UNITED STATES
Doyle, Terrence W., Killingworth, CT, UNITED STATES
King, Ivan, North Haven, CT, UNITED STATES
PI US 2004254103 A1 20041216
US 6855695 B2 20050215
AI US 2003-461282 A1 20030613 (10)
DT Utility
FS APPLICATION
LREP H.D. Coleman, Coleman Sudol Sapone, P.C., 714 Colorado Avenue, Bridgeport, CT, 06605-1601
CLMN Number of Claims: 73
ECL Exemplary Claim: 1
DRWN 15 Drawing Page(s)
LN.CNT 1745
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to compounds according to the structure (I): ##STR1##

Where R is --CH.sub.3 or --CH.sub.2CH.sub.2Cl; R' is C.sub.1-C.sub.7 alkyl or --CH.sub.2CH.sub.2Cl; R.sub.2 or R.sub.4 is OPO.sub.3H.sub.2, NO.sub.2, OCO(Glu-OH), NHCO(Glu-OH), NHR.sub.7 and unassigned groups of R.sub.2, R.sub.3, R.sub.4, R.sub.5 and R.sub.6 are, independently, H, F, Cl, Br, I, OH, OPO.sub.3H.sub.2, OCH.sub.3, CF.sub.3, OCF.sub.3, NO.sub.2, CN, SO.sub.2CH.sub.3, SO.sub.2CF.sub.3, COCH.sub.3, COOCH.sub.3, SCH.sub.3, SF.sub.5, NH.sub.2, NHR.sub.7, N(CH.sub.3).sub.2, OPO.sub.3H.sub.2, or a C1-C7 alkyl group with the proviso that when any two of unassigned groups of R.sub.2, R.sub.3, R.sub.4, R.sub.5 or R.sub.6 are other than H, the other two of unassigned groups of R.sub.2, R.sub.3, R.sub.4, R.sub.5 or R.sub.6 are H. R.sub.7 is H or polyglutamyl as described. Phosphoric acid and glutamic acid can be a free acid or pharmaceutically acceptable salt thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 10 OF 17 USPAT2 on STN
AN 2004:321449 USPAT2
TI Water-soluble SHPs as novel alkylating agents
IN Lin, Xu, Brandford, CT, United States
Doyle, Terrence W., Killingworth, CT, United States
King, Ivan, North Haven, CT, United States
PA Vion Pharmaceuticals, Inc., New Haven, CT, United States (U.S. corporation)
PI US 6855695 B2 20050215
AI US 2003-461282 20030613 (10)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Tate, Christopher R.; Assistant Examiner: Ward, Edward
LREP Coleman, Henry D., Sudol, R. Neil, Sapone, William J.
CLMN Number of Claims: 73

ECL Exemplary Claim: 1
DRWN 15 Drawing Figure(s); 15 Drawing Page(s)
LN.CNT 1735
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to compounds according to the structure (I): ##STR1##

Where R is --CH.sub.3 or --CH.sub.2CH.sub.2Cl; R' is C.sub.1-C.sub.7 alkyl or --CH.sub.2CH.sub.2Cl; R.sub.2 or R.sub.4 is OPO.sub.3H.sub.2, NO.sub.2, OCO(Glu-OH), NHCO(Glu-OH), NHR.sub.7 and unassigned groups of R.sub.2, R.sub.3, R.sub.4, R.sub.5 and R.sub.6 are, independently H, F, Cl, Br, I, OH, OPO.sub.3H.sub.2, OCH.sub.3, CF.sub.3, OCF.sub.3, NO.sub.2, CN, SO.sub.2CH.sub.3, SO.sub.2CF.sub.3, COCH.sub.3, COOCH.sub.3, SCH.sub.3, SF.sub.5, NH.sub.2, NHR.sub.7, N(CH.sub.3).sub.2, OPO.sub.3H.sub.2, or a C1-C7 alkyl group with the proviso that when any two of unassigned groups of R.sub.2, R.sub.3, R.sub.4, R.sub.5 or R.sub.6 are other than H, the other two of unassigned groups of R.sub.2, R.sub.3, R.sub.4, R.sub.5 or R.sub.6 are H. R.sub.7 is H or polyglutamyl as described. Phosphoric acid and glutamic acid can be a free acid or pharmaceutically acceptable salt thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 11 OF 17 WPINDEX COPYRIGHT 2008 THE THOMSON CORP on STN
AN 2005-747008 [76] WPINDEX
DNC C2005-227556 [76]
TI Inhibiting tumor cell growth useful for treating cancer e.g. leukemia and lymphoma comprises contacting 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl) hydrazine (VNP40101M) and nucleoside to the tumor cell
DC B05
IN BELCOURT M; KING I; SZNOL M; ZHENG L; ZHENG L M
PA (VION-N) VION PHARM INC; (BELC-I) BELCOURT M; (KING-I) KING I; (SZNO-I) SZNOL M; (ZHEN-I) ZHENG L
CYC 108
PIA WO 2005094282 A2 20051013 (200576)* EN 19[0]
     EP 1804816 A2 20070711 (200746) EN
     CN 101014353 A 20070808 (200805) ZH
     US 20080025984 A1 20080131 (200810) EN
ADT WO 2005094282 A2 WO 2005-US10152 20050325; CN 101014353 A CN 2005-80009262 20050325; EP 1804816 A2 EP 2005-745357 20050325; EP 1804816 A2 WO 2005-US10152 20050325; CN 101014353 A WO 2005-US10152 20050325; US 20080025984 A1 Provisional US 2004-556565P 20040326; US 20080025984 A1 WO 2005-US10152 20050325; US 20080025984 A1 US 2006-593217 20060915
FDT EP 1804816 A2 Based on WO 2005094282 A; CN 101014353 A Based on WO 2005094282 A
PRAI US 2004-556565P 20040326
     US 2006-593217 20060915
AN 2005-747008 [76] WPINDEX
AB WO 2005094282 A2 UPAB: 20060125
 NOVELTY - Inhibiting tumor cell growth comprises contacting 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl)hydrazine (VNP40101M) or its equivalent and a nucleoside or its analog to the tumor cell.
 DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
 (1) inhibiting tumor cell growth comprising contacting VNP40101M or its equivalent; and another anti-tumor therapy to the tumor cell; and
 (2) a composition comprising VNP40101M in combination

with the nucleoside.

ACTIVITY - Cytostatic.

The cytotoxicity of the combination of VNP40101M (0.75 - 6 muM) and Arac (0.75 - 6 muM) on L1210 leukemia was examined using a cell viability assay. Cells were exposed to VNP40101M, alone or in combination with various concentrations of AraC. After 72 hours, the remaining viable cells were quantified by measuring mitochondrial oxidoreductase activity. The results showed a combination index of 0.243 after one hour exposure (0.75 muM Arac and 6 muM VNP40101M used), which indicate strong synergism.

MECHANISM OF ACTION - Tumor cell growth inhibitor.

USE - For treating cancer and tumor (e.g. solid malignant tumor, leukemia (e.g. acute myelogenous leukemia) and lymphoma) (claimed).

ADVANTAGE - The combination of VNP40101M and nucleoside produces synergistic effects in treating tumor.

L4 ANSWER 12 OF 17 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN

AN 2006:109109 BIOSIS

DN PREV200600108639

TI The antineoplastic efficacy of the prodrug Cloretazine (TM) is produced by the synergistic interaction of carbamoylating and alkylating products of its activation.

AU Baumann, Raymond P.; Seow, Helen A.; Shyam, Krishnamurthy; Penketh, Philip G.; Sartorelli, Alan C. [Reprint Author]

CS Yale Univ, Sch Med, Dept Pharmacol, 333 Cedar St, New Haven, CT 06520 USA alan.sartorelli@yale.edu

SO Oncology Research, (2005) Vol. 15, No. 6, pp. 313-325. CODEN: ONREE8. ISSN: 0965-0407.

DT Article

LA English

ED Entered STN: 8 Feb 2006
Last Updated on STN: 8 Feb 2006

AB Cloretazine (TM) {1,2-bis(methylsulfonyl)-1-[(2-chloroethyl)-2-(methylamino)carbonyl]hydrazine; VNP40101M; 101M}) is a sulfonylhydrazine prodrug that possesses broad spectrum antitumor efficacy against transplanted murine and human tumor models and has shown activity in clinical trials against relapsed or refractory acute myeloid leukemia. Base catalyzed activation of this prodrug generates two different reactive intermediates: chloroethylating species that covalently interact with DNA at the O-6-poSition of guanine residues that progress to a G-C interstrand cross-link, and a carbamoylating agent, methyl isocyanate. Previous findings from this laboratory have provided initial evidence that methyl isocyanate can contribute to the efficacy of Cloretazinc (TM) by enhancing the cytotoxicity of the generated chloroethylating species. This action may be due in part to inhibition of the DNA repair protein O-6-alkylguanine-DNA alkyltransferase (AGT); however, activity in cells devoid of AGT indicates that other actions are involved in the synergistic cytotoxicity. Herein we demonstrate that O-6-benzylguanine can also produce synergistic cell kill with the alkylating component of Cloretazine (TM) but differs from methyl isocyanate in that the enhancement occurs in AGT-containing cells, but not in cells devoid of AGT. Methyl isocyanate generated by the decomposition of 1,2-bis(methylsulfonyl)-1[methylaminocarbonyl] hydrazine also acts to enhance the activity of a variety of DNA cross-linking agents, while only producing additive cytotoxicity with methylating agents. How cytometric studies using annexin as a marker for apoptosis indicate that in Chinese hamster ovary cells and in human leukemia cells Cloretazine (TM)-induced apoptosis is primarily caused by the generated methyl isocyanate. Comet assays designed to detect DNA

cross-links in intact cells indicate that the chloroethylating species generated by the activation of Cloretazine (TM) produce DNA cross-links, with the co-generated methyl isocyanate increasing the degree of cross-linking produced by the reactive chloroethylating species. These findings provide further evidence that the methyl isocyanate produced by the activation of Cloretazine (TM) can be a major contributor to the cytotoxicity produced by this antineoplastic agent.

L4 ANSWER 13 OF 17 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
AN 2002:291321 BIOSIS
DN PREV200200291321
TI Toxicological evaluation of 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl)hydrazine (VNP40101M), a novel alkylating agent with potential antitumor activity, with intravenous administration in rats and dogs.
AU Lee, King C. [Reprint author]; Almassian, Bijan; Noveroske, James
CS Aton Pharma, Inc., 777 Old Saw Mill River Road, Tarrytown, NY, 10591, USA klee@atonpharma.com
SO International Journal of Toxicology, (January-February, 2002) Vol. 21, No. 1, pp. 23-38. print.
ISSN: 1091-5818.
DT Article
LA English
ED Entered STN: 15 May 2002
Last Updated on STN: 15 May 2002
AB These studies investigated the toxicological effects of 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl) hydrazine, VNP40101M, a novel alkylating antitumor agent, in animals. Sprague-Dawley rats (2-10/sex/time point at each dose) and Beagle dogs (1-3/sex/time point at each dose) were treated with VNP40101M (0 (vehicle), 1, 3, 10, and 20 mg/kg in rats and 0, 0.3, 1, and 3 mg/kg in dogs), given intravenously (IV, bolus via the tail or slow push via the cephalic or saphenous vein, respectively) once daily for 5 consecutive days. Clinical signs, mortality, body weight, clinical pathology, gross necropsy, organ weights, and histopathology were evaluated for as long as 43 days in rats and 50 days in dogs. In rats, the toxic doses were found to be at 10 and 20 mg/kg, which induced mainly pulmonary toxicity and mortality. The pulmonary toxicity was reflected by an increase in lung weight; clear, pink or red fluid within the thoracic cavity observed at necropsy; and histopathological evidence of alveolar edema, vascular congestion, alveolar histiocytosis, and vascular thrombi. Although some of these effects were observed in rats treated with 3 mg/kg, the incidence was low (apprx7%-30%) and may be reversible (based on the time-dependent reduction in the magnitude of lung weight increases). Therefore, the maximum tolerated dose (MTD, or the maximum dose that did not induce significant toxicity or induced reversible toxicity) was gtoreq3 mg/kg. VNP40101M at 1 mg/kg did not induce any toxicity, other than low incidence of alveolar edema (2/30 rats), and increased incidences of capillary ectasis/congestion and alveolar histocytosis (2-6/30 rats vs. 1/30-36 in control rats). Therefore, the low effect level (LOEL) is considered to be 1 mg/kg in rats when given IV for 5 days. In dogs, LOEL, MTD, and toxic dose levels were comparable (based on a body weight/surface area conversion) to those in rats, except for some gastrointestinal (GI) effects (i.e., red lesion in the ileum) observed at 0.3 mg/kg (equivalent to 1 mg/kg, or similar to the LOEL in rats) and the associated effects (slight body weight loss and inappetence). For dogs treated with 1 mg/kg (equivalent to apprx3 mg/kg, or MTD, in rats), VNP40101M induced the same GI effects seen in dogs treated with 0.3 mg/kg of VNP40101M. Additionally, a transient reduction in white blood

cell counts was also observed. Three mg/kg (equivalent to apprx10 mg/kg, or toxic dose level, in rats) was toxic to dogs, as reflected by the poor clinical condition of these dogs, which subsequently required euthanasia. In conclusion, VNP40101M, when given IV once daily for 5 consecutive days, has a LOEL of 1 mg/kg, a MTD of 3 mg/kg, and toxic doses at gtoreq10 mg/kg in rats. The primary toxicity of VNP40101M was pulmonary toxicity and mortality. Based on an interspecies body weight/surface area conversion, VNP40101M had comparable LOEL (0.3 mg/kg), MTD (1 mg/kg), and toxic doses (gtoreq3 mg/kg) in dogs, except that dogs appeared to be more sensitive to the GI effects of VNP40101M.

L4 ANSWER 14 OF 17 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN
AN 2006024721 EMBASE
TI The antineoplastic efficacy of the prodrug cloretazine® is produced by the synergistic interaction of carbamoylating and alkylating products of its activation.
AU Baumann, Raymond P.; Seow, Helen A.; Shyam, Krishnamurthy; Penketh, Philip G.; Sartorelli, Alan C. (correspondence)
CS Department of Pharmacology and Developmental Therapeutics Program, Cancer Center, Yale University School of Medicine, New Haven, CT 06520, United States. alan.sartorelli@yale.edu
AU Sartorelli, Alan C. (correspondence)
CS Department of Pharmacology, Yale University School of Medicine, 333 Cedar St., New Haven, CT 06520, United States. alan.sartorelli@yale.edu
SO Oncology Research, (2005) Vol. 15, No. 6, pp. 313-325.
Refs: 25
ISSN: 0965-0407 CODEN: ONREE8
CY United States
DT Journal; Article
FS 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 26 Jan 2006
Last Updated on STN: 26 Jan 2006
AB Cloretazine® {1,2-bis(methylsulfonyl)-1-[(2-chloroethyl)-2-(methylamino)carbonyl]hydrazine; VNP40101M; 101M} is a sulfonylhydrazine prodrug that possesses broad spectrum antitumor efficacy against transplanted murine and human tumor models and has shown activity in clinical trials against relapsed or refractory acute myeloid leukemia. Base catalyzed activation of this prodrug generates two different reactive intermediates: chloroethylating species that covalently interact with DNA at the O(6)-position of guanine residues that progress to a G-C interstrand cross-link, and a carbamoylating agent, methyl isocyanate. Previous findings from this laboratory have provided initial evidence that methyl isocyanate can contribute to the efficacy of Cloretazine® by enhancing the cytotoxicity of the generated chloroethylating species. This action may be due in part to inhibition of the DNA repair protein O(6)-alkylguanine-DNA alkyltransferase (AGT); however, activity in cells devoid of AGT indicates that other actions are involved in the synergistic cytotoxicity. Herein we demonstrate that O(6)-benzylguanine can also produce synergistic cell kill with the alkylating component of Cloretazine® but differs from methyl isocyanate in that the enhancement occurs in AGT-containing cells, but not in cells devoid of AGT. Methyl isocyanate generated by the decomposition of 1,2- bis(methylsulfonyl)-1-[methylaminocarbonyl] hydrazine also acts to enhance the activity of a variety of DNA cross-linking agents, while only producing additive cytotoxicity with

methylating agents. Flow cytometric studies using annexin as a marker for apoptosis indicate that in Chinese hamster ovary cells and in human leukemia cells Cloretazine®-induced apoptosis is primarily caused by the generated methyl isocyanate. Comet assays designed to detect DNA cross-links in intact cells indicate that the chloroethylating species generated by the activation of Cloretazine® produce DNA cross-links, with the co-generated methyl isocyanate increasing the degree of cross-linking produced by the reactive chloroethylating species. These findings provide further evidence that the methyl isocyanate produced by the activation of Cloretazine® can be a major contributor to the cytotoxicity produced by this antineoplastic agent. Copyright .COPYRGT. 2005 Cognizant Comm. Corp.

L4 ANSWER 15 OF 17 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN
AN 2002126943 EMBASE
TI Toxicological evaluation of 1,2-Bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl)hydrazine (VNP40101M), a novel alkylating agent with potential antitumor activity, with intravenous administration in rats and dogs.
AU Lee, King C., Dr. (correspondence); Almassian, Bijan; Noveroske, James
CS RAC, Aton Pharma, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591, United States. klee@atonpharma.com
SO International Journal of Toxicology, (2002) Vol. 21, No. 1, pp. 23-38. Refs: 6
ISSN: 1091-5818 CODEN: IJTOFN
CY United States
DT Journal; Article
FS 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
052 Toxicology
LA English
SL English
ED Entered STN: 25 Apr 2002
Last Updated on STN: 25 Apr 2002
AB These studies investigated the toxicological effects of 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl) hydrazine, VNP40101M, a novel alkylating antitumor agent, in animals. Sprague-Dawley rats (2-10/sex/time point at each dose) and Beagle dogs (1-3/sex/time point at each dose) were treated with VNP40101M (0 [vehicle], 1, 3, 10, and 20 mg/kg in rats and 0, 0.3, 1, and 3 mg/kg in dogs), given intravenously (IV, bolus via the tail or slow push via the cephalic or saphenous vein, respectively) once daily for 5 consecutive days. Clinical signs, mortality, body weight, clinical pathology, gross necropsy, organ weights, and histopathology were evaluated for as long as 43 days in rats and 50 days in dogs. In rats, the toxic doses were found to be at 10 and 20 mg/kg, which induced mainly pulmonary toxicity and mortality. The pulmonary toxicity was reflected by an increase in lung weight; clear, pink or red fluid within the thoracic cavity observed at necropsy; and histopathological evidence of alveolar edema, vascular congestion, alveolar histiocytosis, and vascular thrombi. Although some of these effects were observed in rats treated with 3 mg/kg, the incidence was low (.apprx.7%-30%) and may be reversible (based on the time-dependent reduction in the magnitude of lung weight increases). Therefore, the maximum tolerated dose (MTD, or the maximum dose that did not induce significant toxicity or induced reversible toxicity) was ≥3 mg/kg. VNP40101M at 1 mg/kg did not induce any toxicity, other than low incidence of alveolar edema (2/30 rats), and increased incidences of capillary ectasis/congestion and alveolar histocytosis (2-6/30 rats vs.

1/30-36 in control rats). Therefore, the low effect level (LOEL) is considered to be 1 mg/kg in rats when given IV for 5 days. In dogs, LOEL, MTD, and toxic dose levels were comparable (based on a body weight/surface area conversion) to those in rats, except for some gastrointestinal (GI) effects (i.e., red lesion in the ileum) observed at 0.3 mg/kg (equivalent to 1 mg/kg, or similar to the LOEL in rats) and the associated effects (slight body weight loss and inappetence). For dogs treated with 1 mg/kg (equivalent to .apprx.3 mg/kg, or MTD, in rats), VNP40101M induced the same GI effects seen in dogs treated with 0.3 mg/kg of VNP40101M. Additionally, a transient reduction in white blood cell counts was also observed. Three mg/kg (equivalent to .apprx.10 mg/kg, or toxic dose level, in rats) was toxic to dogs, as reflected by the poor clinical condition of these dogs, which subsequently required euthanasia. In conclusion, VNP40101M, when given IV once daily for 5 consecutive days, has a LOEL of 1 mg/kg, a MTD of 3 mg/kg, and toxic doses at ≥10 mg/kg in rats. The primary toxicity of VNP40101M was pulmonary toxicity and mortality. Based on an interspecies body weight/surface area conversion, VNP40101M had comparable LOEL (0.3 mg/kg), MTD (1 mg/kg), and toxic doses (≥3 mg/kg) in dogs, except that dogs appeared to be more sensitive to the GI effects of VNP40101M.

L4 ANSWER 16 OF 17 MEDLINE on STN
AN 2006021874 MEDLINE
DN PubMed ID: 16408696
TI The antineoplastic efficacy of the prodrug Cloretazine is produced by the synergistic interaction of carbamoylating and alkylating products of its activation.
AU Baumann Raymond P; Seow Helen A; Shyam Krishnamurthy; Penketh Philip G; Sartorelli Alan C
CS Department of Pharmacology and Developmental Therapeutics Program, Cancer Center, Yale University School of Medicine, New Haven, CT 06520, USA.
NC CA-90671 (United States NCI)
SO Oncology research, (2005) Vol. 15, No. 6, pp. 313-25.
Journal code: 9208097. ISSN: 0965-0407.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
LA English
FS Priority Journals
EM 200603
ED Entered STN: 14 Jan 2006
Last Updated on STN: 22 Mar 2006
Entered Medline: 21 Mar 2006
AB Cloretazine {1,2-bis(methylsulfonyl)-1-[(2-chloroethyl)-2-(methylamino)carbonyl]hydrazine; VNP40101M; 101M} is a sulfonylhydrazine prodrug that possesses broad spectrum antitumor efficacy against transplanted murine and human tumor models and has shown activity in clinical trials against relapsed or refractory acute myeloid leukemia. Base catalyzed activation of this prodrug generates two different reactive intermediates: chloroethylating species that covalently interact with DNA at the O6-position of guanine residues that progress to a G-C interstrand cross-link, and a carbamoylating agent, methyl isocyanate. Previous findings from this laboratory have provided initial evidence that methyl isocyanate can contribute to the efficacy of Cloretazine by enhancing the cytotoxicity of the generated chloroethylating species. This action may be due in part to inhibition of the DNA repair protein O6-alkylguanine-DNA alkyltransferase (AGT); however, activity in cells devoid of AGT indicates that other actions are involved in the synergistic cytotoxicity. Herein we demonstrate that O6-benzylguanine can also produce synergistic cell kill with the

alkylating component of Cloretazine but differs from methyl isocyanate in that the enhancement occurs in AGT-containing cells, but not in cells devoid of AGT. Methyl isocyanate generated by the decomposition of 1,2-bis(methylsulfonyl)-1-[methylaminocarbonyl]hydrazine also acts to enhance the activity of a variety of DNA cross-linking agents, while only producing additive cytotoxicity with methylating agents. Flow cytometric studies using annexin as a marker for apoptosis indicate that in Chinese hamster ovary cells and in human leukemia cells Cloretazine-induced apoptosis is primarily caused by the generated methyl isocyanate. Comet assays designed to detect DNA cross-links in intact cells indicate that the chloroethylating species generated by the activation of Cloretazine produce DNA cross-links, with the co-generated methyl isocyanate increasing the degree of cross-linking produced by the reactive chloroethylating species. These findings provide further evidence that the methyl isocyanate produced by the activation of Cloretazine can be a major contributor to the cytotoxicity produced by this antineoplastic agent.

L4 ANSWER 17 OF 17 MEDLINE on STN
AN 2002203737 MEDLINE
DN PubMed ID: 11936896
TI Toxicological evaluation of 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl)hydrazine (VNP40101M), a novel alkylating agent with potential antitumor activity, with intravenous administration in rats and dogs.
AU Lee King C; Almassian Bijan; Noveroske James
CS Vion Pharmaceuticals, Inc, New Haven, Connecticut, USA.. klee@atonpharma.com
SO International journal of toxicology, (2002 Jan-Feb) Vol. 21, No. 1, pp. 23-38.
Journal code: 9708436. ISSN: 1091-5818.
CY United States
DT (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200209
ED Entered STN: 9 Apr 2002
Last Updated on STN: 6 Sep 2002
Entered Medline: 5 Sep 2002
AB These studies investigated the toxicological effects of 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylaminocarbonyl) hydrazine, VNP40101M, a novel alkylating antitumor agent, in animals. Sprague-Dawley rats (2-10/sex/time point at each dose) and Beagle dogs (1-3/sex/time point at each dose) were treated with VNP40101M (0 [vehicle], 1, 3, 10, and 20 mg/kg in rats and 0, 0.3, 1, and 3 mg/kg in dogs), given intravenously (IV, bolus via the tail or slow push via the cephalic or saphenous vein, respectively) once daily for 5 consecutive days. Clinical signs, mortality, body weight, clinical pathology, gross necropsy, organ weights, and histopathology were evaluated for as long as 43 days in rats and 50 days in dogs. In rats, the toxic doses were found to be at 10 and 20 mg/kg, which induced mainly pulmonary toxicity and mortality. The pulmonary toxicity was reflected by an increase in lung weight; clear, pink or red fluid within the thoracic cavity observed at necropsy; and histopathological evidence of alveolar edema, vascular congestion, alveolar histiocytosis, and vascular thrombi. Although some of these effects were observed in rats treated with 3 mg/kg, the incidence was low (approximately 7%-30%) and may be reversible (based on the time-dependent reduction in the magnitude of lung weight increases). Therefore, the maximum tolerated dose (MTD, or the maximum dose that did not induce

significant toxicity or induced reversible toxicity) was > or = 3 mg/kg. VNP40101M at 1 mg/kg did not induce any toxicity, other than low incidence of alveolar edema (2/30 rats), and increased incidences of capillary ectasis/congestion and alveolar histocytosis (2-6/30 rats vs. 1/30-36 in control rats). Therefore, the low effect level (LOEL) is considered to be 1 mg/kg in rats when given IV for 5 days. In dogs, LOEL, MTD, and toxic dose levels were comparable (based on a body weight/surface area conversion) to those in rats, except for some gastrointestinal (GI) effects (i.e., red lesion in the ileum) observed at 0.3 mg/kg (equivalent to 1 mg/kg, or similar to the LOEL in rats) and the associated effects (slight body weight loss and inappetence). For dogs treated with 1 mg/kg (equivalent to approximately 3 mg/kg, or MTD, in rats), VNP40101M induced the same GI effects seen in dogs treated with 0.3 mg/kg of VNP40101M. Additionally, a transient reduction in white blood cell counts was also observed. Three mg/kg (equivalent to approximately 10 mg/kg, or toxic dose level, in rats) was toxic to dogs, as reflected by the poor clinical condition of these dogs, which subsequently required euthanasia. In conclusion, VNP40101M, when given IV once daily for 5 consecutive days, has a LOEL of 1 mg/kg, a MTD of 3 mg/kg, and toxic doses at > or = 10 mg/kg in rats. The primary toxicity of VNP40101M was pulmonary toxicity and mortality. Based on an interspecies body weight/surface area conversion, VNP40101M had comparable LOEL (0.3 mg/kg), MTD (1 mg/kg), and toxic doses (> or = 3 mg/kg) in dogs, except that dogs appeared to be more sensitive to the GI effects of VNP40101M.

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	115.82	116.24

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-1.60	-1.60

FILE 'CAPLUS' ENTERED AT 13:45:02 ON 07 MAY 2008

FILE COVERS 1907 - 7 May 2008 VOL 148 ISS 19
FILE LAST UPDATED: 6 May 2008 (20080506/ED)

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=> s King Ivan/AU

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L6          42 KING IVAN/AU

=> s l6 and chloretazine
             0 CHLORETAZINE
L7           0 L6 AND CHLORETAZINE

=> s l7 and cloretazine
            21 CLORETAZINE
L8           0 L7 AND CLORETAZINE

=> s l6 and cloretazine
            21 CLORETAZINE
L9           3 L6 AND CLORETAZINE

=> dis l9 1-3 bib abs

L9   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2008 ACS on STN
AN   2007:922296  CAPLUS
DN   147:356518
TI   Activity of VNP40101M (Cloretazine) in the treatment of CNS
     tumor xenografts in athymic mice
AU   Badruddoja, Michael A.; Keir, Stephen T.; King, Ivan; Zeidner,
     Joseph; Vredenburgh, James J.; Muhlbaier, Lawrence H.; Bigner, Darell D.;
     Friedman, Henry S.
CS   Center for Neurosciences, University of Arizona, Tucson, AZ, 85721, USA
SO   Neuro-Oncology (Durham, NC, United States) (2007), 9(3), 240-244
     CODEN: NEURJR; ISSN: 1522-8517
PB   Duke University Press
DT   Journal
LA   English
AB   VNP40101M, or 1,2-bis(methylsulfonyl)-1-(2-choloro-ethyl)-2-
     (methylamino)carbonylhydrazine (Cloretazine), is a bifunctional
     prodrug that belongs to a class of DNA-modifying agents-the
     sulfonylhydrazines-that has been synthesized and been shown to have
     activity against a wide spectrum of xenografts.  The current study was
     designed to assess the activity of VNP40101M administered at a dose of 18
     mg/kg daily for five days against a panel of human adult and pediatric CNS
     tumors growing s.c. or intracranially in athymic nude mice.  The results
     demonstrated statistically significant (p < 0.05) growth delays of 15.0,
     8.3, 51.0, 60+, 60+, and 60+ days in s.c. xenografts derived from
     childhood glioblastoma multiforme (D-456 MG), childhood ependymoma (D-528
     EP and D-612 EP), childhood medulloblastoma (D-425 MED), and adult
     malignant glioma (D-245 MG and D-54 MG), resp., with corresponding tumor
     regressions in 10 of 10, 4 of 10, 8 of 10, 9 of 10, 9 of 10, and 10 of 10
     treated mice, resp.  Delayed toxicity was seen more than 60 days after
     treatment, with 23 deaths in 100 treated animals, despite a median weight
     loss of only 0.06%.  In mice bearing intracranial D-245 MG xenografts,
     treatment with VNP40101M at a dose of 18 mg/kg daily for five days
     produced a 50% increase in median survival compared with controls.  Addnl.
     expts. conducted against s.c. D-245 MG xenografts by using reduced doses
     of 13.5 or 9.0 mg/kg daily for five days demonstrated tumor growth delays
     of 82.2 and 53.5 days, with corresponding tumor regressions in 8 of 9 and
     9 of 10 treated mice, resp. (all values, p < 0.001), with one toxic death.
     These findings suggest that VNP40101M is active in the treatment of a wide
     range of human central nervous system tumors and warrants translation to
     the clinic.
RE.CNT  15    THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9   ANSWER 2 OF 3  CAPLUS  COPYRIGHT 2008 ACS on STN
AN   2007:447320  CAPLUS
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DN 147:180783
TI Anti-tumor efficacy of Cloretazine (VNP40101M) alone and in combination with fludarabine in murine tumor and human xenograft tumor models
AU Zheng, Li-mou; Li, Zujin; Liu, Lanzhen; Song, Bai Louis; King, Ivan
CS Vion Pharmaceutical, Inc., New Haven, CT, 06511, USA
SO Cancer Chemotherapy and Pharmacology (2007), 60(1), 45-51
CODEN: CCPHDZ; ISSN: 0344-5704
PB Springer
DT Journal
LA English
AB Cloretazine (VNP40101M), a new sulfonylhydrazine alkylating agent, has demonstrated broad-spectrum anti-tumor activity in preclin. studies. In this study, Cloretazine was evaluated both as a monotherapy and in combination with fludarabine in murine tumor and human tumor xenograft models. Cloretazine significantly inhibited the growth of s.c. implanted tumors, including B16F10 murine melanoma in C57BL/6 mice, and H460 human lung carcinoma and WiDr human colon carcinoma in athymic nude CD1 mice. The inhibition of tumor growth by Cloretazine was dose dependent, increasing from 42.2 to 87% as the dose escalated from 100 to 150 mg/kg. Cloretazine showed equivalent efficacy but lower toxicity compared to cyclophosphamide in these models. The combination therapy, consisting of a single dose of 10 mg/kg Cloretazine plus five doses of 70 mg/kg fludarabine, given every other day i.p., significantly increased the long-term survival of BDF1 mice bearing the L1210 murine leukemia. On Day 65 post-tumor implantation, the combination therapy yielded a 90% survival rate compared to 40% for Cloretazine alone and 0% for fludarabine alone.
RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:1103438 CAPLUS
DN 143:360090
TI Cloretazinetm (VNP40101M) combination with a nucleoside/nucleoside analog for cancer treatment
IN King, Ivan; Sznol, Mario; Belcourt, Michael; Zheng, Li-Mou
PA Vion Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005094282	A2	20051013	WO 2005-US10152	20050325
	WO 2005094282	A3	20060511		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1804816	A2	20070711	EP 2005-745357	20050325
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,				

IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR
CN 101014353 A 20070808 CN 2005-80009262 20050325
US 20080025984 A1 20080131 US 2006-593217 20060915
PRAI US 2004-556565P P 20040326
WO 2005-US10152 W 20050325
AB The invention provides a method for treating tumor in a subject comprising administering to the subject an effective amount of (1) VNP40101M, or its equivalent; and (2) a nucleoside, or a nucleoside analog. The invention also provides a method for inhibiting tumor cell growth comprising contacting the tumor cell with effective amts. of: (1) VNP40101M, or its equivalent; and (2) a nucleoside, or a nucleoside analog. The invention relates to the treatment of cancer, comprising administering to a subject in need thereof an effective amount of VNP40101M in combination with a nucleoside.

=> s Sznol Mario/AU
L10 30 SZNOL MARIO/AU

=> s l10 and cloretazine
21 CLORETAZINE
L11 2 L10 AND CLORETAZINE

=> dis l11 1-2 bib abs

L11 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:1191211 CAPLUS
DN 144:285703
TI Phase I Study of Cloretazine (VNP40101M), a Novel Sulfonylhydrazine Alkylating Agent, Combined with Cytarabine in Patients with Refractory Leukemia
AU Giles, Francis; Verstovsek, Srdan; Thomas, Deborah; Gerson, Stanton; Cortes, Jorge; Faderl, Stefan; Ferrajoli, Alessandra; Ravandi, Farhad; Kornblau, Steven; Garcia-Manero, Guillermo; Jabbour, Elias; O'Brien, Susan; Karsten, Verena; Cahill, Ann; Yee, Karen; Albitar, Maher; Sznol, Mario; Kantarjian, Hagop
CS Department of Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA
SO Clinical Cancer Research (2005), 11(21), 7817-7824
CODEN: CCREF4; ISSN: 1078-0432
PB American Association for Cancer Research
DT Journal
LA English
AB Purpose: Cloretazine (VNP40101M) is a novel sulfonylhydrazine alkylating agent with significant antileukemia activity. A phase I study of cloretazine combined with cytarabine (1-β-D-arabinofuranosylcytosine, ara-C) was conducted in patients with refractory disease. Design: Ara-C was given i.v. at a fixed dose of 1.5 gm/m2/d by continuous infusion for 4 days (patients ages <65 years at time of diagnosis) or 3 days (patients ages ≥65 years). Cloretazine was given i.v. over 15 to 60 min on day 2 at a starting dose of 200 mg/m2, with escalation in 100 mg/m2 increments in cohorts of three to six patients until a maximum tolerated dose was established. The DNA repair enzyme O6-alkylguanine DNA alkyltransferase (AGT) was measured at baseline. Results: Forty patients, including 32 with acute myeloid leukemia, received 47 courses of treatment. Complete responses were seen at cloretazine dose levels of ≥400 mg/m2 in 10 of 37 (27%) evaluable patients, and in this patient subset, AGT activity was significantly lower in patients that responded to treatment than in patients who did not ($P \leq 0.027$). Dose-limiting toxicities (gastrointestinal and myelosuppression) were seen with 500 and 600 mg/m2 of cloretazine combined with the 4-day ara-C schedule

but not seen with the 3-day schedule. Conclusion: The recommended cloretazine dose schedule for future studies is 600 mg/m2 combined with 1.5 gm/m2/d continuous infusion of ara-C for 3 days. The cloretazine and ara-C regimen has significant antileukemic activity. AGT activity may be a predictor of response to cloretazine.

RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:1103438 CAPLUS
DN 143:360090
TI Cloretazinetm (VNP40101M) combination with a nucleoside/nucleoside analog for cancer treatment
IN King, Ivan; Sznol, Mario; Belcourt, Michael; Zheng, Li-Mou
PA Vion Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005094282	A2	20051013	WO 2005-US10152	20050325
	WO 2005094282	A3	20060511		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1804816	A2	20070711	EP 2005-745357	20050325
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
	CN 101014353	A	20070808	CN 2005-80009262	20050325
	US 20080025984	A1	20080131	US 2006-593217	20060915
PRAI	US 2004-556565P	P	20040326		
	WO 2005-US10152	W	20050325		

AB The invention provides a method for treating tumor in a subject comprising administering to the subject an effective amount of (1) VNP40101M, or its equivalent; and (2) a nucleoside, or a nucleoside analog. The invention also provides a method for inhibiting tumor cell growth comprising contacting the tumor cell with effective amts. of: (1) VNP40101M, or its equivalent; and (2) a nucleoside, or a nucleoside analog. The invention relates to the treatment of cancer, comprising administering to a subject in need thereof an effective amount of VNP40101M in combination with a nucleoside.

=> s Belcourt Michael/AU
L12 6 BELCOURT MICHAEL/AU

=> dis l12 1-6 bib abs

L12 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:1103438 CAPLUS
DN 143:360090

TI Cloretazinetm (VNP40101M) combination with a nucleoside/nucleoside analog for cancer treatment
IN King, Ivan; Sznol, Mario; Belcourt, Michael; Zheng, Li-Mou
PA Vion Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005094282	A2	20051013	WO 2005-US10152	20050325
	WO 2005094282	A3	20060511		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1804816	A2	20070711	EP 2005-745357	20050325
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
	CN 101014353	A	20070808	CN 2005-80009262	20050325
	US 20080025984	A1	20080131	US 2006-593217	20060915
PRAI	US 2004-556565P	P	20040326		
	WO 2005-US10152	W	20050325		

AB The invention provides a method for treating tumor in a subject comprising administering to the subject an effective amount of (1) VNP40101M, or its equivalent; and (2) a nucleoside, or a nucleoside analog. The invention also provides a method for inhibiting tumor cell growth comprising contacting the tumor cell with effective amts. of: (1) VNP40101M, or its equivalent; and (2) a nucleoside, or a nucleoside analog. The invention relates to the treatment of cancer, comprising administering to a subject in need thereof an effective amount of VNP40101M in combination with a nucleoside.

L12 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:191780 CAPLUS
TI Hypoxia-selective anticancer agents: Phosphate derivatives of KS119 (VNP40119)
AU Lin, Xu Kevin; Belcourt, Michael; Zheng, Li-Mou; Clairmont, Caroline; Nassar, Ala; Doyle, Terrence W.; King, Ivan
CS Vion Pharmaceuticals Inc, New Haven, CT, 06511, USA
SO Abstracts of Papers, 229th ACS National Meeting, San Diego, CA, United States, March 13-17, 2005 (2005), MEDI-447 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69GQMP
DT Conference; Meeting Abstract
LA English
AB It has been increasingly of interest that hypoxia-selective drugs play pos. roles in combining treatment with other clin. drug(s) or radiation for cancer therapy. More recently, we have developed a lead compound KS119 to address its hypoxia-selectivity from the class of the sulfonylhydrazine prodrugs (SHPs). In this unique sulfonylhydrazine class, CLORETAZINETM had been exhibited to be a novel alkylating agent for cancer therapy in Phase II human clin. trials; and it had been granted orphan drug designation from the FDA for treatment of acute myelogenous leukemia

(AML). In this presentation, design and synthesis of two lead series of phosphate derivs. (KS119W and KS119S) of KS119 will be shown. Preclin. investigation has demonstrated that these newly synthesized anticancer agents are highly hypoxia-selective and have a promising activity of tumor inhibition in vivo with excellent pharmaceutical and pharmacokinetic properties. These phosphate derivs. of KS119 are optimized to give a clin. candidate.

L12 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:169181 CAPLUS
DN 139:300968
TI Tumor-selective Salmonella-based cancer therapy
AU Bermudes, David; Low, K. Brooks; Pawelek, John; Feng, Ming; Belcourt, Michael; Zheng, Li-Mou; King, Ivan
CS Vion Pharmaceuticals, Inc., New Haven, CT, 06511, USA
SO Biotechnology & Genetic Engineering Reviews (2001), 18, 219-233
CODEN: BGERES; ISSN: 0264-8725
PB Intercept Ltd.
DT Journal; General Review
LA English
AB A review of tumor-selective Salmonella-based cancer therapy includes subtopics of (1) introduction (2) genetic methods for generation of tumor-specific strains (3) antitumor efficacy of VNP 20009 (4) tumor-specific prodrug -converting enzyme delivery (5) antitumor effects of Salmonella in combination with radiation (6) conclusions.
RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:526744 CAPLUS
DN 138:247993
TI Tumor-targeted Salmonella expressing cytosine deaminase as an anticancer agent
AU King, Ivan; Bermudes, David; Lin, Stanley; Belcourt, Michael; Pike, Jeremy; Troy, Kimberly; Le, Trung; Ittensohn, Martina; Mao, John; Lang, Wenshang; Runyan, Jacob D.; Luo, Xiang; Li, Zujin; Zheng, Li-Mou
CS Vion Pharmaceuticals, Inc., New Haven, CT, 06511, USA
SO Human Gene Therapy (2002), 13(10), 1225-1233
CODEN: HGTHE3; ISSN: 1043-0342
PB Mary Ann Liebert, Inc.
DT Journal
LA English
AB The study was designed to evaluate whether TAPET-CD, an attenuated strain of Salmonella typhimurium expressing Escherichia coli cytosine deaminase (CD), was capable of converting nontoxic 5-fluorocytosine (5-FC) to the active antitumor agent 5-fluorouracil (5-FU). The antitumor effect of TAPET-CD plus 5-FC against s.c. implanted colon tumors was also evaluated. TAPET-CD was given to tumor-bearing mice by a single bolus i.v. administration followed with 5-FC by i.p. administration. TAPET-CD accumulated in tumors at levels 1000-fold higher than that in normal tissues and high levels of 5-FU were detected in tumors in mice treated with both TAPET-CD and 5-FC. No 5-FU could be detected in normal tissues. Inhibition of tumor growth was observed in mice treated with either TAPET-CD alone or TAPET-CD in combination with 5-FC (TAPET-CD/5-FC), but not with 5-FC alone. TAPET-CD/5-FC inhibited tumor growth by 88%-96%, compared to TAPET-CD alone, which inhibited tumor growth by 38%-79%. These data suggest that tumor-targeting Salmonella could be used to deliver prodrug-converting enzyme selectively to tumors and produced anti-tumor effects when the corresponding prodrug was also given.
RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2001:265561 CAPLUS
DN 134:290399
TI Compositions and methods for tumor-targeted delivery of effector molecules
IN Bermudes, David G.; King, Ivan C.; Clairmont, Caroline A.; Lin, Stanley L.; Belcourt, Michael
PA Vion Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 185 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001025397	A2	20010412	WO 2000-US23242	20000824
	WO 2001025397	A3	20020124		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2386465	A1	20010412	CA 2000-2386465	20000824
	AU 2000069334	A	20010510	AU 2000-69334	20000824
	AU 783714	B2	20051201		
	EP 1261369	A2	20021204	EP 2000-957764	20000824
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	JP 2004500042	T	20040108	JP 2001-528552	20000824
	BR 2000014491	A	20040309	BR 2000-14491	20000824
	NZ 518354	A	20050225	NZ 2000-518354	20000824
	US 6962696	B1	20051108	US 2000-645415	20000824
	MX 2002PA03384	A	20020820	MX 2002-PA3384	20020403
	US 20040229338	A1	20041118	US 2003-738423	20031216
	US 20050249706	A1	20051110	US 2005-82544	20050317
	US 20070298012	A1	20071227	US 2007-627743	20070126
PRAI	US 1999-157500P	P	19991004		
	US 1999-157581P	P	19991004		
	US 1999-157637P	P	19991004		
	US 2000-645415	A3	20000824		
	WO 2000-US23242	W	20000824		
	US 2003-738423	A1	20031216		

AB The present application discloses the preparation and use of attenuated tumor-targeted bacteria vectors for the delivery of one or more primary effector mol.(s) to the site of a solid tumor. The primary effector mol(s). of the invention is used in the methods of the invention to treat a solid tumor cancer such as a carcinoma, melanoma, lymphoma, or sarcoma. The invention relates to the surprising discovery that effector mols., which may be toxic when administered systemically to a host, can be delivered locally to tumors by attenuated tumor-targeted bacteria with reduced toxicity to the host. The application also discloses the delivery of one or more optional effector mol.(s) (termed secondary effector mols.) which may be delivered by the attenuated tumor-targeted bacteria in conjunction with the primary effector mol.(s).

L12 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1989:626082 CAPLUS

DN   111:226082
OREF 111:37409a,37412a
TI   Enhancer and silencerlike sites within the transcribed portion of a Ty2 transposable element of Saccharomyces cerevisiae
AU   Farabaugh, Philip; Liao, Xiao Bei; Belcourt, Michael; Zhao, Hong; Kapakos, James; Clare, Jeffrey
CS   Dep. Biol. Sci., Univ. Maryland, Catonsville, MD, 21228, USA
SO   Molecular and Cellular Biology (1989), 9(11), 4824-34
     CODEN: MCEBD4; ISSN: 0270-7306
DT   Journal
LA   English
AB   The Ty2-917 element is a member of the Ty2 class of retroviruslike transposable elements of S. cerevisiae. Regions downstream of the Ty2-917 transcription start site modulate its transcription. One region was located downstream of the transcription initiation site (position 240) and within the first 559 base pairs of the element. This region had a dramatic effect, causing an approx. 1000-fold increase in steady-state levels of RNA. The region stimulated transcription when placed in either orientation upstream of a heterologous gene, HIS4, lacking its own upstream activation sequence (UAS). This pos. acting region was termed an enhancer, by analogy to sites described in higher cells, to distinguish it from yeast UASs which do not function when placed within the transcribed portion of the gene. Though, like some higher eukaryotic enhancers, the Ty2-917 enhancer is located within the transcribed region, it is unlike them in that it occurs within a coding region rather than in an intron. The Ty2-917 enhancer and the Ty2-917 UAS had a synergistic effect on transcription, together stimulating transcription 15-fold over the predicted additive effect. The authors also identified a site which decreases RNA accumulation, located about 750 base pairs into the element. This site functioned in only one orientation when inserted upstream of the UAS-less heterologous gene. The site was similar to silencers, or neg. enhancers, in that it acted to repress transcription from outside the transcribed region, but was distinct in that the function of a canonical silencer was independent of orientation.

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=> s Zheng Li-Mou/AU
L13         32 ZHENG LI-MOU/AU

=> s l13 and choretazine
             0 CHORETAZINE
L14          0 L13 AND CHORETAZINE

=> s l13 and cloretazine
            21 CLORETAZINE
L15          2 L13 AND CLORETAZINE

=> dis l15 1-2 bib abs

L15  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2008 ACS on STN
AN   2007:447320  CAPLUS
DN   147:180783
TI   Anti-tumor efficacy of Cloretazine (VNP40101M) alone and in combination with fludarabine in murine tumor and human xenograft tumor models
AU   Zheng, Li-mou; Li, Zujin; Liu, Lanzhen; Song, Bai Louis; King, Ivan
CS   Vion Pharmaceutical, Inc., New Haven, CT, 06511, USA
SO   Cancer Chemotherapy and Pharmacology (2007), 60(1), 45-51
     CODEN: CCPHDZ; ISSN: 0344-5704
PB   Springer
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DT Journal
LA English
AB Cloretazine (VNP40101M), a new sulfonylhydrazine alkylating agent, has demonstrated broad-spectrum anti-tumor activity in preclin. studies. In this study, Cloretazine was evaluated both as a monotherapy and in combination with fludarabine in murine tumor and human tumor xenograft models. Cloretazine significantly inhibited the growth of s.c. implanted tumors, including B16F10 murine melanoma in C57BL/6 mice, and H460 human lung carcinoma and WiDr human colon carcinoma in athymic nude CD1 mice. The inhibition of tumor growth by Cloretazine was dose dependent, increasing from 42.2 to 87% as the dose escalated from 100 to 150 mg/kg. Cloretazine showed equivalent efficacy but lower toxicity compared to cyclophosphamide in these models. The combination therapy, consisting of a single dose of 10 mg/kg Cloretazine plus five doses of 70 mg/kg fludarabine, given every other day i.p., significantly increased the long-term survival of BDF1 mice bearing the L1210 murine leukemia. On Day 65 post-tumor implantation, the combination therapy yielded a 90% survival rate compared to 40% for Cloretazine alone and 0% for fludarabine alone.
RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:1103438 CAPLUS
DN 143:360090
TI Cloretazinetm (VNP40101M) combination with a nucleoside/nucleoside analog for cancer treatment
IN King, Ivan; Sznol, Mario; Belcourt, Michael; Zheng, Li-Mou
PA Vion Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005094282	A2	20051013	WO 2005-US10152	20050325
	WO 2005094282	A3	20060511		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1804816	A2	20070711	EP 2005-745357	20050325
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
	CN 101014353	A	20070808	CN 2005-80009262	20050325
	US 20080025984	A1	20080131	US 2006-593217	20060915
PRAI	US 2004-556565P	P	20040326		
	WO 2005-US10152	W	20050325		

AB The invention provides a method for treating tumor in a subject comprising administering to the subject an effective amount of (1) VNP40101M, or its equivalent; and (2) a nucleoside, or a nucleoside analog. The invention also provides a method for inhibiting tumor cell growth comprising contacting the tumor cell with effective amts. of: (1) VNP40101M, or its equivalent; and

(2) a nucleoside, or a nucleoside analog. The invention relates to the treatment of cancer, comprising administering to a subject in need thereof an effective amount of VNP40101M in combination with a nucleoside.

=> dis hist

(FILE 'HOME' ENTERED AT 13:39:43 ON 07 MAY 2008)

FILE 'APOLLIT, BABS, CAPLUS, CBNB, CIN, COMPENDEX, DISSABS, EMA, IFIPAT, NTIS, PASCAL, PROMT, RAPRA, SCISEARCH, TEXTILETECH, USPATFULL, USPATOLD, USPAT2, WPIFV, WPINDEX, WSCA, WTEXTILES, BIOSIS, EMBASE, MEDLINE' ENTERED AT 13:41:01 ON 07 MAY 2008

L1 0 S VNP40110M
L2 17 S METHYLAMINOCARBONYL(A)HYDRAZINE
L3 17 S L2 AND VNP40101M
L4 17 S L3 AND (TUMOR OR ANTITUMOR)
L5 2 S L4 AND NUCLEOSIDE

FILE 'CAPLUS' ENTERED AT 13:45:02 ON 07 MAY 2008

L6 42 S KING IVAN/AU
L7 0 S L6 AND CHLORETAZINE
L8 0 S L7 AND CLORETAZINE
L9 3 S L6 AND CLORETAZINE
L10 30 S SZNOL MARIO/AU
L11 2 S L10 AND CLORETAZINE
L12 6 S BELCOURT MICHAEL/AU
L13 32 S ZHENG LI-MOU/AU
L14 0 S L13 AND CHORETAZINE
L15 2 S L13 AND CLORETAZINE

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